

PATENT

Atty. Docket: 409251  
Express Mail Label No. EL 820325895 US

PROCESS FOR THE PREPARATION OF CYCLOHEXANOL DERIVATIVES

Related Applications

**[0001]** This application claims benefit of priority to application serial number 02153015.7 filed November 29, 2002 in the People's Republic of China and is a continuation-in-part of that application.

BACKGROUND OF THE INVENTION

**[0002]** A number of nontricyclic antidepressants have recently been developed to treat depression and anti-social disorders. One of these compounds, Venlafaxine, chemically named (+)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol, is widely used. The manufacturing cost of Venlafaxine is relatively high.

**[0003]** Literature reports including EP 0112669B and US 4,535,186 describe the preparation of cyclohexanol derivatives as intermediates for making Venlafaxine. A variety of  $\alpha$ -aryl- $\alpha$ -(1-hydroxylcyclohexyl) ethylamine derivatives are synthesized by reacting  $\alpha$ -aryl acetonitriles or  $\alpha$ -aryl-N,N-dimethyl acetamides with cyclohexanone. The reactions are performed using organo-lithium metal compounds of nitriles or amides, which are reacted with cyclohexanone using tetrahydrofuran as solvent at a low temperature below -50°C. The yield is reported to be less than 50%. It is costly and difficult to run large scale commercial production at reaction temperatures below -50°C.

**[0004]** United States Patent 5,043,466 describes another process of preparing  $\alpha$ -aryl- $\alpha$ -(1-hydroxylcyclohexyl) ethylamine derivatives. In that process,  $\alpha$ -aryl- $\alpha$ -(1-hydroxylcyclohexyl) acetonitriles or  $\alpha$ -aryl-N,N-dimethyl (1-hydroxylcyclohexyl) acetamides are reacted with organic alkali metal compounds, such as lithium, sodium, potassium, or magnesium halide, to form a carbanion in a mixed solvent including 80-100% (w/w) of one or more hydrocarbons and 0-20% (w/w) of one or more ethers at -40°C to about 40°C. This organo metallic complex is then reacted with cyclohexanone to prepare  $\alpha$ -aryl- $\alpha$ -(1-hydroxylcyclohexyl) ethylamine derivatives. The use of n-butyllithium is a great inconvenience in large-scale operation because butyllithium is a highly hazardous chemical.

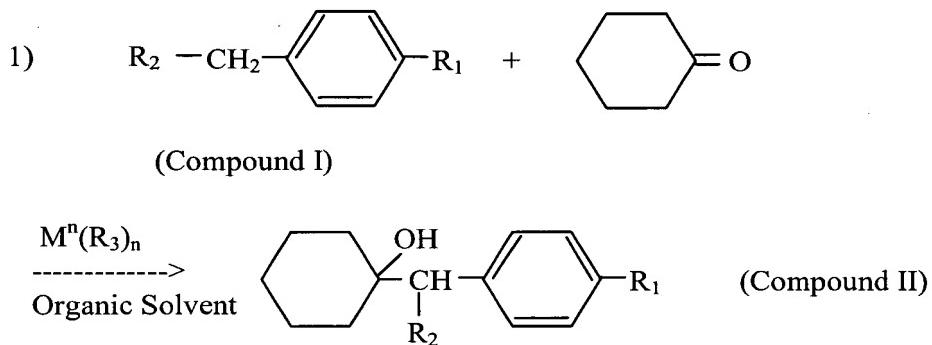
**[0005]** A more recent patent, US 6,504,044, reports another method for preparing 1-[cyano(aryl)methyl] cyclohexanol by reacting cyclohexanone with aryl acetonitrile in the presence of sodium hydroxide or potassium hydroxide. Although the low reaction temperature has been avoided, the use of strong bases such as sodium hydroxide renders the procedure more complicated and costly in large scale production. Moreover, the use of relatively expensive phase transfer catalysts such as n-butyl ammonium iodide adds significantly to the cost of production. In the absence of phase transfer catalysts, the yield of the process disclosed in US 6,504,044 is significantly reduced.

**[0006]** There remains a need to provide more economical processes for preparing Venlafaxine intermediates which do not require facilitation by phase transfer catalysts and can be carried out under milder conditions more suitable for large scale production.

#### SUMMARY

**[0007]** The present disclosure advances the art and overcomes the problems outlined above by providing a process of making intermediates for nontricyclic antidepressants, such as Venlafaxine and the like. The process is advantageously capable of avoiding low process temperatures, as well as avoiding use of phase transfer catalysts and butyllithium in the manufacture of Venlafaxine and its derivatives.

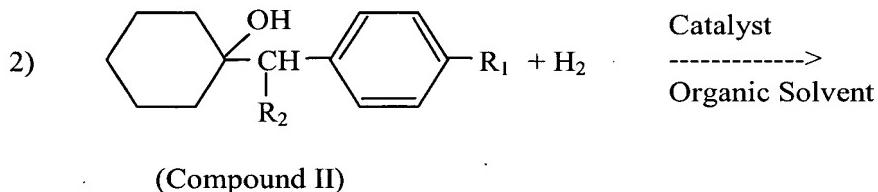
**[0008]** Venlafaxine intermediates of interest include cyclohexanol derivatives, such as N,N-dimethyl-2-(1-hydroxylcyclohexyl)-2-(4-hydroxylphenyl) ethylamine, or N,N-dimethyl-2-(1-hydroxylcyclohexyl)-2-(4-methoxylphenyl) ethylamine, and salts thereof. Once obtained, these intermediates may be used to manufacture Venlafaxine, for example, as described in US 5,043,466. In one embodiment, a process of making the intermediates includes reacting a para-substituted aryl compound with cyclohexanone in the presence of an alkali metal hydride or other organic compound to form a bridged cyclohexyl-phenyl composition according to Equation (1) below:

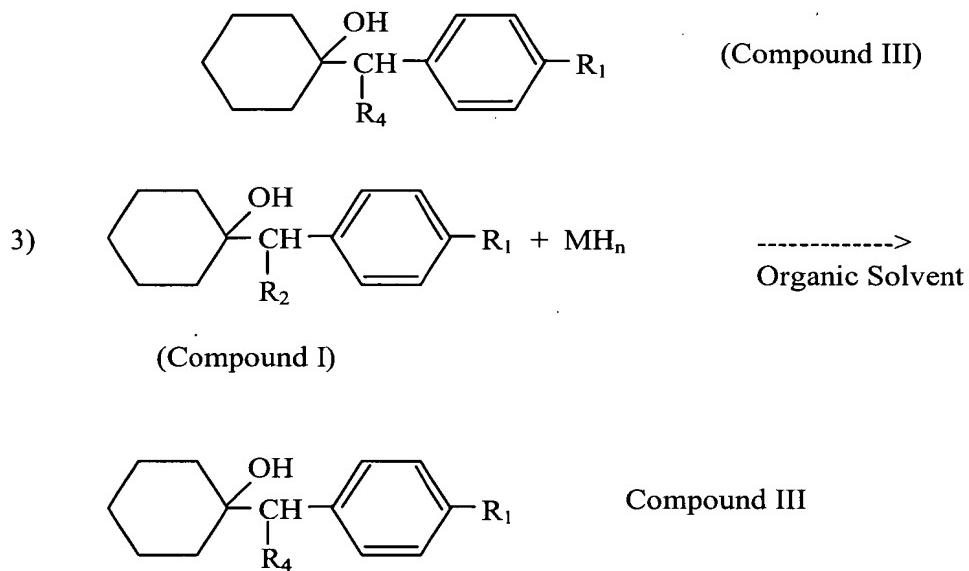


wherein  $\text{R}_1$  is OH or  $\text{OCH}_3$ ;  $\text{R}_2$  is CN,  $\text{CONH}_2$ ,  $\text{CONHCH}_3$  or  $\text{CON}(\text{CH}_3)_2$ ;  $\text{R}_3$  is H; M denotes an alkali metal or complex metal, e.g.,  $\text{M}_1\text{M}_2$  where  $\text{M}_1$  and  $\text{M}_2$  are different metals; and n is the net oxidation state of M. When M includes lithium,  $\text{R}_3$  may also be an organic ligand, such as an amine having a carbon number from 2 to 6, and the use of lithium diisopropylamide (diisopropylamino lithium) is particularly preferred.

**[0009]** The reaction according to Equation (1) is performed using organic solvents and appropriate reaction conditions, taking care to minimize or eliminate water from the reaction solution because water degrades the compound  $\text{M}^n(\text{R}_3)_n$ . Materials suitable for use as  $\text{M}^n(\text{R}_3)_n$  include, for example, NaH, KH, LiH, MgH<sub>2</sub>, CaH<sub>2</sub>, AlH<sub>3</sub>, and LiAlH<sub>4</sub>. The reaction temperature ranges, in a preferred sense, from -10°C to 30°C. The organic solvents may include commercially available solvents, such as alkanes and aryl compositions. By way of example, n-hexane, toluene, or a mixture thereof are suitable for use as the organic solvents.

**[0010]** Compound II may be further reduced to form other intermediates, as shown below in Equations (2) and (3), respectively





wherein R<sub>1</sub> is OH or OCH<sub>3</sub>; R<sub>2</sub> is CN, CONH<sub>2</sub>, CONHCH<sub>3</sub> or CON(CH<sub>3</sub>)<sub>2</sub>; and R<sub>4</sub> denotes CH<sub>2</sub>NH<sub>2</sub>. M and n are defined above. In context of Equation (3), for example, MH<sub>n</sub> is preferably AlH<sub>3</sub> and/or LiAlH<sub>4</sub>.

**[0011]** The reactions according to Equations (2) and (3) are both performed using organic solvents under appropriate reaction conditions to reduce Compound II. In the reaction according to Equation (2), Raney nickel is used as a catalyst, while the reaction according to Equation (3) is performed using a hydride including one or more elements from Groups 1A and 3A of the Periodic table as a reducing agent, for example, aluminum hydride or lithium aluminum hydride as a reducing agent.

**[0012]** The foregoing reactions are preferably but optionally conducted at a temperature ranging from -10°C to 30°C, and more preferably from -10°C to 10°C.

**[0013]** Where diisopropylamino lithium is used in Equation (1), the reaction temperature is suitably from -10°C to 50°C, and the diisopropylamino lithium solution may be obtained by reacting metallic lithium with phenethylene. In the case of a lithium reagent, the organic solvent may be, for example, a mixture of ether and aromatic hydrocarbon, such as toluene or styrene. The ether may be, for example, diethyl ether, diisopropyl ether, ethylene glycol dimethyl ether, and tetrahydrofuran.

[0014] Solvents for use according to Equations (2) and (3) may be an alcohol or a mixture of different alcohols. Reaction temperatures for these reduction reactions may range, for example, from 0°C to 40°C. Catalytic hydrogenation facilitated by Rainey nickel may be done under atmospheric pressure. AlH<sub>3</sub> used in Equation (3) may be obtained by reacting lithium aluminum hydride (LiAlH<sub>4</sub>) with anhydrous aluminum chloride in an ether solvent.

#### DETAILED DESCRIPTION

[0015] There will now be shown, by way of nonlimiting examples, a process of making Compound II, as shown in Equation (1) above. The process uses readily available organic solvents and an alkali metal hydride or an organic alkali metal compound such as organo-lithium to prepare Compound II. The two methods to prepare Compound II are discussed below. The general concepts and instrumentalities are illustrated by detailed examples, which embody specific implementation of the general concepts and instrumentalities and should not be construed as setting a limit to the scope of the processes.

[0016] The reaction between Compound I and cyclohexanone according to Equation (1) occurs in the presence of a base, such as NaH, KH, LiH, MgH<sub>2</sub>, CaH<sub>2</sub>, AlH<sub>3</sub>, and LiAlH<sub>4</sub> at a temperature ranging from -10°C to 30°C. The process utilizes commercially available solvents, for example, n-hexane and toluene. The reaction advantageously occurs over a short reaction period, produces high yields (~80%) and incurs lower raw material costs, when compared with prior methods. Compound II may be isolated in high yield by precipitation from the organic solvent.

[0017] When the composition M<sup>n</sup>(R<sub>3</sub>)<sub>n</sub> is an organolithium, the organic solvent provides a reductive solvent atmosphere that is well suited for the reaction between Compound I and cyclohexanone in which phenylethylene, metal lithium and diisopropylamine are used to form a lithium diisopropylamine solution in ethylbenzene, Compound I and cyclohexanone is thereafter added to produce Compound II.

[0018] The reactions according to Equations (2) and (3) provide two alternative processes for the preparation of intermediates having the formula of

Compound III by reduction of Compound II, for example, using Raney Nickel or aluminum hydride. These two methods are described below.

**[0019]** Equation (2) shows the use of a Raney nickel catalyst and supplemental hydrogen to reduce Compound II to Compound III in an alcohol based solvent environment at a temperature ranging, in a preferred sense, from about 0°C to 30°C.

**[0020]** Equation (3) shows reduction of Compound II using aluminum hydride to form Compound III in a mixed solvent system. AlH<sub>3</sub> is prepared by the reaction of anhydrous aluminum chloride with lithium aluminum hydride in a mixed solvent system at room temperature.

**[0021]** A process is also described for the preparation of an acid salt of Compound III. Venlafaxine can be produced from either Compound III or the acid salt of Compound III.

#### EXAMPLE 1

##### Preparation of 1-[Cyano(p-methoxyphenyl)methyl]cyclohexanol (Compound II)— Method I—Use of Sodium Hydride

**[0022]** A reaction mixture was prepared by sequentially combining 10mL of n-hexane, 10mL of toluene and 710mg of sodium hydride (60%, 17.8mmol) in a dry flask. The mixture was stirred for 15 minutes at room temperature. A 2.5g (17.0mmol) quantity of p-methoxyphenylacetonitrile was slowly added to the reaction mixture over a 10 minute interval. The reaction mixture was stirred for 50 minutes at room temperature.

**[0023]** The reaction mixture was cooled to -5°C, a 2.18g (22.0mmol) of cyclohexanone was added dropwise over 10 minutes. The reaction mixture was stirred for 5 hours to the reaction end point, which was monitored by thin layer chromatography (TLC) using a solvent of ligroin: ethyl acetate=4:1. Reaction was deemed complete when only one spot was detected using TLC. At completion of the reaction, a quantity of 5% diluted hydrochloric acid was added dropwise to adjust pH to 6-7, and the mixture was stirred for 15 minutes. Precipitate was filtered under vacuum, and the filter cake was washed with water. The filter cake was dried to obtain a crude sample.

[0024] The crude sample was purified by recrystallization using a volume of toluene in milliliters equal to three times the crude product weight in grams. A 3.33g quantity of the purified product, 1-[Cyano(p-methoxyphenyl) methyl] cyclohexanol (Compound II) was obtained, representing an 80% yield. Composition of the reaction product was initially confirmed by melting point, which was assessed at mp. 124-125°C. A melting point of 123-126°C for this product is published in the literature.

[0025] Composition of the final reaction product was further confirmed using infrared spectroscopy (IR), nuclear magnetic resonance (NMR) and mass spectroscopy (MS), which produced these results:

IR:  $3494\text{cm}^{-1}$  ( ν O-H),  $2935\text{cm}^{-1}$  ( ν O-H),  $2240\text{cm}^{-1}$  ( ν CN),  $1612\text{cm}^{-1}$  ( ν Aromatic ring),  $1512\text{cm}^{-1}$  ( ν Aromatic ring);

$^1\text{H-NMR}(\text{CDCL}_3, \text{TMS})$ : δ 7.26ppm (d, 2 H, Ar H), δ 6.89ppm (d, 2 H, Ar H), 3.8ppm(s, 3 H, OCH<sub>3</sub>), 3.73ppm (s, 1 H, CHCN), 1.73-1.17ppm (m, 10 H, Cyclohexyl H), ( $^1\text{H-NMR}(\text{CDCL}_3)$ ): δ 7.32ppm and 6.95ppm (q, 4 H, Ar H), 3.8ppm(s, 3 H, OCH<sub>3</sub>), 3.76ppm (s, 1 H, CHCN), 1.56ppm(m, 10 H, Cyclohexyl H in Literature);

MS: m/z 245 (M+; EIMS)( CIMS m/e= M<sup>+</sup>+1=246 in Literature).

## EXAMPLE 2

### Preparation of 1-[Cyano(p-methoxyphenyl)methyl]cyclohexanol (Compound II)— Method II—Use of Diisopropylamino Lithium

[0026] A reaction mixture was prepared by sequentially mixing 2500mL of absolute ether, 1250mL of diisopropylamine and 50g of metal lithium (in plate form) into a 5000mL three-necked round-bottomed flask under dry nitrogen. The reaction mixture was heated for reflux using a water-bath. A mixture of 464mL of phenylethylene

dissolved in absolute ether was added dropwise to the reaction mixture, which was refluxed for 2 hours. The lithium plates completely reacted to form a gray solution.

**[0027]** The reaction mixture was cooled below 5°C. A solution including 680mL of p-methoxyphenylacetonitrile (5mol, diluted with 400mL of toluene) and 550mL of cyclohexanone (5.3mol, diluted with 300mL of toluene) was added dropwise to the reaction mixture. A green-yellowish solution was obtained. The solution was poured into a mixture of 1kg of ice and 600mL of concentrated hydrochloric acid to form a precipitate. The precipitate was isolated by filtration to yield 610g of crude product. The filtrate was separated by phase, and the organic layer was concentrated by vacuum to obtain an additional other 190g of the crude product. The total quantity of crude product was 800g, for a yield of 65%. The crude product was purified using toluene recrystallization, as in Example 1, to obtain 600g of final product, 1-[Cyano(p-methoxyphenyl)methyl] cyclohexanol (Compound II). Purity was confirmed by melting point, which was determined as mp.124-126°C, as well as IR, NMR, and MS.

### EXAMPLE 3

#### Preparation of 1-[2-Amino-1-(p-methoxyphenyl)ethyl] cyclohexanol (Compound III) and Its Salts

##### Method 1—Use of Rainey Nickel

**[0028]** A 2.45g(10mmol) quantity of the 1-[cyano(p-methoxyphenyl)methyl] cyclohexanol obtained in Example 1 and 1.0g of catalyst Raney Nickel were dispersed to a 50mL flask containing 30mL of methanol. Air was purged from the flask four times with hydrogen. The mixture was stirred vigorously at room temperature under a blanket of hydrogen for about 15 hours to complete the reaction. The reaction progress was periodically monitored using TLC, and was deemed complete when no more hydrogen was being absorbed and only one spot was detected on the TLC plate.

**[0029]** After completion of the reaction, stirring stopped and the reaction mixture stood. A precipitate formed. The reaction mixture was filtered to remove the precipitate as a filter cake. The Rainey nickel was removed from the filter cake. The filter cake was then washed 3 times with methanol. The methanol wash was combined

wit the supernatant from the reaction mixture. Methanol was removed by vacuum distillation to leave 2.50g of an oily crude reaction product, which was purified using silica gel column chromatography ( $\text{CH}_2\text{Cl}_2:\text{MeOH}=30:1$  v/v). A 2.06g quantity of 1-[2-Amino-1-(p-methoxyphenyl)ethyl] cyclohexanol was obtained to provide an 83% yield. TLC analysis of the final product using as a solvent  $\text{CH}_2\text{Cl}_2:\text{MeOH}=30:10$  v/v produced one primary spot, confirming the purity of the reaction product. This intermediate can be directly used for preparing Venlafaxine and its salts.

#### EXAMPLE 4

##### Preparation of 1-[2-Amino-1-(p-methoxyphenyl)ethyl] cyclohexanol (Compound III) and Its Salts

###### Method 2—Use of Lithium Aluminum Hydride

**[0030]** A 100g quantity of  $\text{LiAlH}_4$  and 1500mL of absolute ether were added into a 5000mL flask to prepare a reaction mixture at room temperature. A solution was prepared with 125g of anhydrous aluminum trichloride ( $\text{AlCl}_3$ ) into 600 ~ 1000mL of absolute ether under nitrogen, and added dropwise to the reaction mixture. The reaction mixture was cooled in an ice-water bath. A solution containing 314g of 1-[Cyano(p-methoxyphenyl)methyl] cyclohexanol obtained in Example 1 dissolved in 800 mL of tetrahydrofuran (THF) was added dropwise to the reaction mixture. The reaction mixture thus formed was allowed to react for 5 hours at room temperature. A 400mL quantity of THF: $\text{H}_2\text{O}$  (1:1) was added, followed by 400~600mL of 50% saturated sodium hydroxide ( $\text{NaOH}$ ) solution until the resulting solid-liquid had clearly separated and the solid appeared white. The liquid organic layer was decanted, and the remaining precipitate was washed with ether. The remaining precipitate was combined with the decanted organic layer and concentrated by vacuum to obtain an oily product which was 1-[2-Amino-1-(p-methoxyphenyl)ethyl] cyclohexanol. TLC analysis produced a single spot, ninhydrin positive, using a solvent of chloroform-methanol-acetic acid (80: 10: 10 v/v). This oily product can be directly used for preparing Venlafaxine HCl.

### EXAMPLE 5

#### Preparation of 1-[2-Amino-1-(p-methoxyphenyl)ethyl] cyclohexanol (Compound III) and Its Salts

##### Method 3—Preparation of 1-[2-Amino-1-(p-methoxyphenyl)ethyl] cyclohexanol (Compound III) Hydrochloride

**[0031]** A 1.0g of the crude product obtained in Example 4 was dissolved in 2mL of methanol at room temperature in a 10mL conical flask. The mixture was cooled in an ice-water bath and stirred. Hydrogen chloride gas was added to the reaction flask until the gas was no longer introduced under stirring. Ether was added dropwise until some slight turbidity was observed. Stirring ceased, and the mixture stood for 10 hours. 860mg of white solid is precipitated. Initial purity and composition were confirmed by melting point, which was determined to be m. p. =168-170°C (168-172°C is reported in the Literature). Composition was confirmed to be Compound III hydrochloride by IR and NMR:

IR:  $3364\text{cm}^{-1}$  ( ν N-H),  $2933\text{cm}^{-1}$  ( ν O-H),  $1611\text{cm}^{-1}$  ( ν Aromatic ring),  
 $1512\text{cm}^{-1}$  ( ν Aromatic ring).

$^1\text{H-NMR}(\text{CDCL}_3, \text{TMS})$ :  $\delta$  7.09ppm (d, 2 H, Ar H),  $\delta$  6.76ppm (d, 2 H, Ar H),  
3.70ppm (s, 3 H,  $\text{OCH}_3$ ), 3.16ppm (dd, 1 H, CH), 3.04ppm (dd, 1 H, CH),  
2.57ppm (m, 3 H, CH and  $\text{NH}_2$ ), (m, 10 H, Cyclohexyl H), ( $^1\text{H-NMR}$  (DMSO-d6  
in Literature):  $\delta$  7.85ppm (s, 3 H,  $\text{NH}_3^+$ ), 3.75ppm (s, 3 H,  $\text{OCH}_3$ ), 3.20ppm (m, 3  
H,  $\text{CHCH}_2$ ), 1.35ppm (m, 10 H, Cyclohexyl H).